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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,487	10/29/2003	Peter C. Baciu		7399

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Carlos A. Fisher
ALLERGAN, INC.
T2-7H
2525 Dupont Drive
Irvine, CA 92612

EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 08/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/697,487	BACIU ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/29/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 11-17 are pending and under examination.

2. It is improper to recite "agents" in claim 11, line 1as the claims should recite the singular form. It is suggested that the word be changed to "an agent".

3. Claims 16-17 are objected to because they depend from canceled claim 1 and should be written as an independent claim.

4. Claims 11- 17 are objected to because the "α subunit" in claim 1, lines 3, 6, 8, claim 13 and 17 and "alpha subunit" claims 12, 15, 16 and 17 are used interchangeably. Consistency is required.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 11-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for a method for screening agents which inhibit an angiogenic response comprising a) contacting: I) an inactive pro form or convertase-activated form of an integrin α subunit involved in angiogenesis, ii) an agent to be tested for the ability to inhibit angiogenesis and iii) metalloprotease MT1-MMP, under conditions promoting an increase in activation of the integrin a subunit in the absence of said agent, and b) correlating inhibition of said increase in integrin a subunit activation with the ability of the agent to inhibit angiogenesis in claim 11, wherein the correlating step is accomplished by observing a difference in migration of the activated form versus the inactive form of the alpha subunit in electrophoresis or chromatography in claim 12, in which the alpha subunit comprises the αv subunit in claim 17. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The claims are broadly drawn to screening agents that inhibit angiogenesis which effect the activation of alpha subunits and therefore inhibit angiogenesis.

This includes screening for a whole universe of agents which bind to or effect any pro form or convertase-activated form of integrin alpha subunits. This further includes screening of any alpha integrin subunit.

There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the alpha subunits recited in the instant claims. A person of skill in the art would not know which alpha integrin subunit are essential, which alpha integrin subunits are non-essential. There is insufficient guidance to direct a person of skill in the art to select particular alpha integrin subunit as essential for inhibiting angiogenesis dependent VEGF. Without detailed direction as to which alpha integrin subunits are essential to the angiogenesis, a person of skill in the art would not be able to determine without undue experimentation which of the those alpha integrin subunits encompassed by the instant claims would share the ability to inhibit angiogenesis. The specification lacks sufficient guidance as to which integrin alpha subunit is involved in angiogenesis when contacted with MT1-MMP. For example, Bergeron et al (Biochemical J, 2003) teach that only nine out of the 18 α subunits (α3, α4, α5, α6, α7, α8, αv, αE, and αIIb) undergo post-translational endoprpteolytic cleavage at a site comprised of pairs of basic amino acids (see introduction, 2nd paragraph). Further, while the specification discloses that α2β1 integrin is localized to the developed vasculature bed, Ratnikov et al (J Biol. Chem. 277:7377-7385, 2002) teach that MT1-MMP cleaves αv, α3 and α5 but not α2 integrin subunit (see page 7381, 2nd col., 1st paragraph). Without sufficient guidance to which alpha integrin subunit can be used in the screening method with the claimed activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The specification discloses (pages 8-11) the expression pattern of integrin and MMP expression within the corneal alkaline burn model relative to the angiogenic response using RT-PCR, immunoflouorescence and gelatin zymograph. The specification on page 9, lines 10-15, and page 31, lines 4-15, concluded that the integrin expression during neovascularization of rat corneas in response to alkaline injury is restricted to angiogenesis along the VEGF/αvβ3 pathway in conjunction with α1β1, α2β1 and α5β1integrins, wherein the α1β1, α2β1 and α5β1integrin showed consistent localization to the developing vasculature bed.

However, Zhang *et al* (Invest Ophthalmol Vis Sci. 2002 Apr;43(4):955-62) teach that in several instances in which VEGF is present, both αvβ3 and αvβ3 are expressed, and in at least one study it was shown that the functional significance of αvβ3-mediated angiogenesis may reflect the presence of ligand for αvβ3. However, not all aspects of angiogenesis are dependent on expression of αvβ3 or αvβ5 integrins. Knockout mice for αv and β3 integrins appear to undergo extensive vasculogenesis and angiogenesis (see page 955, 1st col., 1st ¶ to the 2nd col. 1st ¶). Zhang *et al* further teach that pharmaceutical intervention with αvβ3 antagonists has no effect on the angiogenic response (see page 955, 2nd col., 2nd ¶). Zhang *et al* concluded that in the alkaline-burn-induced corneal angiogenesis model, αvβ3 does not appear to play a major role in mediating the angiogenic response, and thus the role of MT1-MMP and MMP-2 within this model may be outside their association with αvβ3 (see page 961, 1st col., 2nd).

One cannot extrapolate the teachings of the specification to the scope of the claims because the method claims are drawn to screening agents which inhibit angiogenesis comprising contacting an inactive pro form or convertase-activated form of any α integrin subunit without the biological properties representative of what is claimed and applicant has not enabled any of alpha integrin subunits because it has not been shown that α3, α5 and αv integrin subunits (know to be cleaved by MT1-MMP) are capable of functioning in mediating the angiogenic response. There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability of any activated α subunit by cleavage of the pro form using MT1-MMP to promote angiogenesis in the absence of inhibitors (agents).

The specification does not provide sufficient guidance on the effect of MT1-MMP, which function as an integrin convertase, on all the α integrin subunit. There is insufficient guidance in the specification with regard to the generation of activated form of α integrin subunit via the MT1-MMP-dependent pathway. The specification does not provide information or shows that MT1-MMP can process all claimed proα subunit into an active α subunit.

Applicant's disclosure appears to be inconsistent with the results provided by these post-filing date references. Thus faced with contradictory and seemingly mutually exclusive results regarding the role of αv or any integrin alpha subunit that can be cleaved by the MT1-MMP on the angiogenic response, the lack of empirical data of screening using any activated α subunit by MT1-MMP effect on angiogenesis, and the lack of any effect of any agent on the integrin dependent angiogenesis, undue experimentation would be required of the skilled artisan to determine the whether activated αv (or any alpha subunit) by MT1-MMP has a role in angiogenesis in view of the instant disclosure. While the level of skill of in the art may be high, the state of the prior art is that it is in fact unknown and untested what are the underlying alpha subunits effects on the angiogenesis response.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

8. Claims 11-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is not in possession of a method for screening agents which inhibit an angiogenic response comprising a) contacting: I) an inactive pro form or convertase-activated form of an integrin α subunit involved in angiogenesis, ii) an agent to be tested for the ability to inhibit angiogenesis and iii) metalloprotease MT1-MMP, under conditions promoting an increase in activation of the integrin a subunit in the absence of said agent, and b) correlating inhibition of said increase in integrin a subunit activation with the ability of the agent to inhibit angiogenesis in claim 11, wherein the correlating step is accomplished by observing a difference in migration of the activated form versus the inactive form of the alpha subunit in electrophoresis or chromatography in claim 12, in which the alpha subunit comprises the αv subunit in claim 17.

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (an integrin α subunit that is cleavable by MT1-MMP) to describe the claimed genus, nor does it provide a description of structural features that are common to species (an integrin α subunit that is cleavable by MT1-MMP). The specification provides no structural description of any integrin α subunit that is cleavable by MT1-MMP other than αv; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed cleavable α subunits by MT1-MMP look like. The specification's disclosure is inadequate to describe the claimed genus of an integrin α subunit.

Applicant has disclosed αv integrin subunit as the principal integrin associated with endothelial cells within the corneal alkaline burn model of inflammatory mediated angiogenesis; therefore, the skilled artisan cannot envision all the contemplated alpha subunit possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she]

invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 11 and 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Klotz *et al* (Graefes Arch Clin Exp Ophthalmol. 238(1):88-93, January 2000), as is evidenced by Zhang *et al* (Invest Ophthalmol Vis Sci. 2002 Apr;43(4):955-62).

Klotz *et al* teaches a method to asses therapeutic potential (screening) of alpha(v)-integrin antagonists LM609 and cRGDfV (agents) in neovascularization (angiogenesis) of the anterior segment, their inhibitory effect on angiogenesis was studied in two rat models for corneal neovascularization (within a cell). Klotz et al further teach that In corneas with silver nitrate burns, systemic cRGDfV treatment showed no significant reduction of vascularization compared with controls and that pellets containing bFGF and LM609 mAb induced significatntly less neovasculaization than pellets containing bFGF and control mAb (the resolution step). While Klotz et al is silent with regard to contacting with MTI-MMP, the corneal neovascularization express MT1-MMP as is evidenced by Zhang *et al.* Zhang et al examined the pattern of integrin and MMP expression within the corneal alkaline burn model relative to the angiogenic response by RT-PR, immunohistology, and gelactinase zymography. Zhang et al teach that MT1-MMP expression correlated with the angiogenic response.

Claims 15-16 are included because Zhang et al teaching that MT1-MMP express within the corneal neovascularization, then the activation of the αv by MT1-MMP by cleavage of the pro form of αv is considered inherent property. Further, since the method is within a cell then a change in glycolsylation of the pro form of αv is also considered inherent property.

The reference teachings anticipate the claimed invention.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klotz *et al*, as is evidenced by Zhang *et al*, in view of Deryugina *et al* (2000) (IDS Ref No.AB).

The teachings of Klotz *et al*, and the evidentiary reference Zhang *et al* have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation that the correlating step is accomplished by observing a difference in migration of the activated form versus the inactive form of the alpha subunit in electrophoresis in claim 12, and the MT1-MMP and pro form of the integrin α subunit are recombinantly expressed within the same cell in claim 13.

Deryugina *et al* (2000) teach that MTI-MMP is capable of activating αvβ3 by cleavage of the β3 subunit when breast cells are transfected with MTI-MMP and the αvβ3 subunit (see pag. Deryugina *et al* further teach that to address the functional cooperation of MT1-MMP and integrin αvβ3 contributes to the invasive phenotype of tumor cells, a stable transfection of human MCF7 breast carcinoma cell with both MTI-MMP and β3 (see abstract in particular). In addition, Deryugina *et al* teach that the MT1-MMP-dependent functional activation of αvβ3 correlates with modification(s) of the β3 subunit, including its higher electrophoretic mobility and affected the LM609-binding site (see abstract in particular). Finally, Deryugian *et al* concluded that these mechanisms are considered to be applicable in a variety of physiological processes involving cell migration and invation such as noevascularization (see page 22 last paragraph in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to express the recombinantly express MT1-MMp and pro form of the integrin a subunit within the same cell and use the electrophoretic mobility to observe the difference in migration of the activated from versus the inactive form as taught by Deryugina *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because recombinant expression provides high levels of expression and the electrophoretic mobility provides a MT1-MMP-dependent functional activation of αvβ3 correlation with the modification as taught by Deryugina *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
August 20, 2004

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600